Articles

Staphylococcus aureus Septic Arthritis in Patients on Hemodialysis Treatment

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We retrospectively reviewed hospital discharge diagnoses of septic arthritis over an 11-year period (1982 through 1992) at 3 medical centers; 11 episodes of septic arthritis were identified in patients on hemodialysis treatment. Of the 11 episodes, 9 were caused by *Staphylococcus aureus*; in 8 of 9, the blood cultures were positive for the organism and the infection was monoarticular. Concurrent infection of the dialysis access site occurred in 4 cases. Two patients died (22%). We postulate that repeated skin trauma and contact with health care personnel and facilities result in a high rate of nasal carriage of *S aureus* and, hence, an increased risk of bacteremia with its attendant complications such as septic arthritis. The use of mupirocin nasal ointment is reported to eradicate or suppress carriage in a high percentage of patients; some studies report that long-term suppressive therapy reduces the frequency of *S aureus* bacteremia.

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A case of a patient on hemodialysis treatment in whom *Staphylococcus aureus* septic arthritis developed prompted inquiry into the regional frequency of this serious disorder. Only one previous article has addressed this subject.[1] At three large tertiary care centers, nine patients with this disease were identified over an 11-year period. Septic arthritis is a complication of *S aureus* bacteremia that in turn results from a high rate of nasal and skin carriage of *S aureus*. The literature indicates that the frequency of invasive *S aureus* disease in dialysis-dependent patients may be reduced substantially by appropriate antimicrobial prophylaxis.

Patients and Methods

Patient hospital discharge records with ICD-9 [*International Classification of Diseases*, 9th revision] codes for septic arthritis and hemodialysis were searched over an 11-year period (1982 through 1992) at three local tertiary care medical centers: Providence Medical Center, Good Samaritan Hospital and Medical Center, and Oregon Health Sciences University Medical Center, Portland. In all, 11 episodes of septic arthritis in 10 patients on hemodialysis treatment were identified, 9 of which were caused by *S aureus*. Patient records were analyzed for patient demographics, joints involved, microbiologic data, length of time on hemodialysis, type of dialysis access, evidence of concurrent infection of the dialysis access site, a history of previous *S aureus* infection(s), management of the infection, and patient outcome.

Summaries of Selected Cases

Patient 1

The patient, an 81-year-old woman with diabetes mellitus and ischemic cardiomyopathy, had been on hemodialysis treatment for eight months when malaise developed without localizing symptoms or signs. Four days later, she presented to the emergency department with pain in her right arm, and analgesics were administered. The following day she was admitted to the hospital with fever, left arm and shoulder pain, and fluctuance of the left shoulder. Cultures of left shoulder joint fluid and blood were positive for *S aureus*, and an initial therapy regimen of vancomycin hydrochloride and gentamicin sulfate was changed to nafcillin sodium and rifampin. Despite appropriate antibiotic therapy, the patient gradually became hypotensive and died in septic shock on the fourth hospital day.

Patient 2

The patient, a 61-year-old woman on hemodialysis therapy for many years, had a flulike illness with an increase in chronic arthralgias of her hips, shoulders, and knees. She had previously had multiple infections of the polytetrafluoroethylene arteriovenous dialysis access graft of her left forearm, including two episodes of *S aureus* bacteremia. Although the old graft was still present, a new graft had been placed in the right forearm six weeks before admission. Two days after her flulike illness began, she was admitted to the hospital. Blood cultures

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obtained on admission were subsequently positive for *S aureus* resistant in vitro only to penicillin G. Because of an allergy to penicillin and cephalosporins, a regimen of vancomycin was started. Persistent fever and positive blood cultures over the next six days prompted removal of the graft despite the absence of physical findings; culture of specimens obtained intraoperatively grew *S aureus*. Arthralgias and fever persisted; three weeks after admission, the right shoulder was aspirated and the aspirate grew *S aureus*. Daily shoulder arthrocentesis yielded culture-positive specimens for the next five days. For this reason, gentamicin was added to the regimen of vancomycin, and this therapy was continued for nine days as the patient's temperature and leukocyte count returned to normal. Subsequently, the gentamicin therapy was stopped, but vancomycin was continued for a total of six weeks after the initial shoulder aspiration. The patient was discharged after a 2½-month hospital stay.

Patient 3

This 57-year-old woman with end-stage renal disease had a first polytetrafluoroethylene dialysis access graft placed in her left forearm. The graft clotted, and a thrombectomy was done a week after placement. The surgical wound continued to drain, and two months later she was admitted to the hospital with a wound infection, bacteremia, and left lower lobe pneumonia due to *S aureus*. She complained of left anterior chest pain, but no physical signs other than chest wall tenderness were found. On the fifth hospital day, a fluctuant mass was seen over the left sternoclavicular joint. Purulent fluid was aspirated, and the cultures grew *S aureus*. The patient was initially treated with cefazolin for five days; subsequently, she was switched to vancomycin, which was continued for six weeks. In addition, the infected portion of the graft was excised.

Results

Nine episodes of *S aureus* septic arthritis in eight dialysis patients are summarized in Table 1. Three patients had arteriovenous fistulas, four had polytetrafluoroethylene (Gore-Tex) arteriovenous grafts, and one had a cuffed dialysis catheter (Perma-Cath). Concurrent access infection was documented in four cases; three of these involved polytetrafluoroethylene grafts, and one involved a cuffed catheter. In another patient, *S aureus* infection of the arteriovenous fistula occurred 2½ months before an admission for septic arthritis. The access did not appear infected at the time of the episode of septic arthritis; however, no blood cultures were done to definitively exclude this source. In the other eight episodes, blood cultures grew *S aureus*. Two patients died of *S aureus* sepsis, one on the fourth hospital day and one on the tenth hospital day, for a mortality of 22%. The six surviving patients received courses of intravenous antibiotics ranging from one week to six weeks. All *S aureus* isolates were methicillin-sensitive. The choice of antibiotics varied, but in most cases consisted of a β-lactam plus an aminoglycoside for early therapy, followed by a longer course of a β-lactam or vancomycin. Four patients had previous admissions for *S aureus* infections, including five episodes of bacteremia and one of infection of the arteriovenous fistula in which concurrent blood cultures were sterile. The two patients who died had been on hemodialysis treatment a relatively short period of time (2 months and 8 months), and this was their first *S aureus* infection. None of the patients had nasal or skin cultures for the identification of *S aureus* carriage, and none were on prophylactic antibiotic regimens designed to decrease the risk of *S aureus* infections.

TABLE 1.—*Characteristics of 8 Hemodialysis Patients With 9 Episodes of* Staphylococcus aureus *Arthritis*

Characteristic	*Patients, No.*	*Episodes, No.*
Sex		
Male	3	
Female	5	
Age range, yr	57-81	
Time on dialysis	?days to 14 years	
Joints affected		
Monoarticular		8
Biarticular		1
Above diaphragm		8
(Shoulder)		(3)
(Sternoclavicular)		(2)
(Wrist)		(2)
(Acromioclavicular)		(1)
Below diaphragm		2
(Ankle)		(1)
(Wrist)		(1)
Blood culture results		
Positive for *S aureus*		8
Not done		1
Concurrent dialysis access infection		4
Surgical incision and drainage		4
Multiple aspirations		3
Predominant antimicrobial therapy		
Vancomycin ± aminoglycoside ± rifampin	7*	
Nafcillin plus rifampin	1†	
Cefazolin only	1	

*One of the 7 patients died.
†Patient died.

Discussion

In our review of hospital discharges for septic arthritis, we were struck by the clustering of cases in patients on long-term hemodialysis therapy and by the predominance of *S aureus* as the etiologic agent. We then sought episodes of septic arthritis in hemodialysis patients at two other tertiary care medical centers. Over an 11-year period, 9 of 11 joint infections were due to *S aureus*. The high mortality (22%), protracted hospital stays, and paucity of previous reports in the literature stimulated inquiry into whether it is possible to reduce the risk of this serious illness.

We found one published study of septic arthritis in hemodialysis patients.[1] Six cases of septic arthritis were reported in five patients; *S aureus* was the pathogen in four.

Blood cultures grew *S aureus* in three patients, and the access device grew *S aureus* in the fourth. Five of the six joints infected with *S aureus* were above the diaphragm. Three patients had previous infections of the access site. Two of the patients had several previous episodes of *S aureus* infection. All patients in this series survived.

Admissions for septic arthritis in the series described in the previous paragraph made up 2% of all admissions of patients on hemodialysis therapy during the study period. In comparison, admissions for septic arthritis are much less common in nondialyzed patients. In one report, hospital admissions for all patients at King County and Seattle, Washington, Veterans Affairs hospitals during a five-year period were reviewed, and an overall incidence of septic arthritis of 0.022% was found.[2]

We reviewed the literature to identify some of the reasons for the increased incidence of joint infections in patients on hemodialysis therapy and for the preponderance of *S aureus*. Hematogenous seeding is the most common pathogenesis of joint infection.[3] Hemodialysis patients have frequent vascular access infections[4-10] and, hence, have a greater risk of their joints becoming infected. In addition, hemodialysis patients are reported to have a high incidence of joint calcification and other abnormalities such as hemarthrosis and chronic capsulitis.[11] A diseased joint may be more susceptible to invasion when bacteremia occurs. The reason for a predisposition for infection in joints above the diaphragm in these patients is unclear. Perhaps it reflects "downstream" embolization in some cases. We were unable to correlate clearly the location of arteriovenous access to involved joints, however.

The incidence of bacteremia due to all organisms varies from 0.7 to 1.5 episodes per 100 patient-dialysis months.[4-10,12,13] The percentage due to *S aureus* varied from 32% to 80%. The dialysis access site is incriminated as the primary source of infection in 49% to 100% of the episodes. *Staphylococcus aureus* is the most frequent organism cultured from the blood, representing 32% to 80% of the bacteremic episodes. In contrast, *S aureus* accounts for only 11% of community-acquired and 20% of hospital-acquired cases of bacteremia in all patients.[14] The reported mortality for all cases of bacteremia is about 20%, and for *S aureus* bacteremia it is similar at 8% to 16%. Of those patients with bacteremia, 3% or less suffer hematogenous septic arthritis.[10] Other frequently encountered hematogenous complications include pulmonary emboli (3.5% to 16%), empyema (1% to 2.7%), and central nervous system infections (2% to 4.5%). Of interest, infective endocarditis is reported in only 3.5% to 9%.[8-10] Hence, *S aureus* infection, including septic arthritis, is a major risk for patients on hemodialysis.

Colonization of the nose and skin (including the vascular dialysis access site) is the presumed portal of entry for *S aureus*. Repeated skin trauma, contact with colonized hospital personnel, the presence of a foreign body, and possibly immune defects are proposed explanations for the high rate of colonization. Once the skin barrier is broken, the clearance of transient bacteremia may be impaired in a patient with uremia. For example, macrophage Fc receptors bind immunoglobulin G-coated organisms, and these receptors are substantially impaired in patients with uremia.[15]

Numerous studies have reported an increased rate of staphylococcal nasal colonization in patients on hemodialysis treatment. Nasal colonization rates in these patients are reported to vary between 40% and 81% as compared with 20% to 40% carriage rates among nondialyzed patients.[5,6,16-20] *Staphylococcus aureus* colonization rates of patients undergoing continuous ambulatory peritoneal dialysis are reported to be between 39% and 45%.[21,22] Hence, 40% or more of all dialysis patients are at risk for invasive *S aureus* disease.

Hemodialysis patients who are *S aureus* carriers have more staphylococcal infections than noncarriers. In a retrospective study of 40 patients, 10 of the 14 with *S aureus* colonization (71%) had serious staphylococcal infections, although only 10 of 26 patients (38%) without colonization had staphylococcal infections.[23] In a prospective study of *S aureus* carriage in hemodialysis patients, 7 *S aureus* infections occurred in 31 carriers (22%) versus 2 infections in 19 noncarriers (11%).[16] In a second prospective controlled trial, a 46% incidence of *S aureus* infections was reported in carriers versus 11.5% in noncarriers ($P < .01$). The phage type of the infecting organism matched the carriage organism in 93% of the carriers in whom infection developed.[18] Hence, it seems reasonable to consider possible ways of preventing or controlling the magnitude of *S aureus* colonization.

Prevention

Invasive disease could be prevented in one of several ways: preventing *S aureus* colonization, eradicating existing colonization, or decreasing the density (and, it is hoped, the invasion risk) of colonizing *S aureus*. A variety of agents, both oral and topical, have been used to try to eradicate staphylococcal nasal and skin carriage. Topical gentamicin sulfate, vancomycin hydrochloride, and bacitracin and oral cloxacillin sodium, tetracycline, cephalexin hydrochloride, and erythromycin are ineffective.[24] Intravenous vancomycin is likewise ineffective.[18] In contrast, oral rifampin, in combination with topical bacitracin, reduces the short-term incidence of both *S aureus* nasal carriage and *S aureus* infections.[18] Unfortunately, rifampin possesses several features that make it less attractive as a prophylactic agent. It can be hepatotoxic, it stains body secretions orange, and when used intermittently, it can be associated with flulike symptoms. In addition, the use of rifampin alone is known to induce resistance in most bacterial species.

Topical mupirocin (pseudomonic acid) has shown promise as an agent for suppressing or eliminating the nasal carriage of both methicillin-sensitive and resistant *Staphylococcus aureus* in a variety of populations (Table 2). It was applied two to four times a day for three to five days, and at the end of therapy, negative cultures were reported in 74% to 100% of one study group. For as long as three months after treatment, the percentage of patients with persistent eradication ranged from 41% to 82%.[19,25-29]

TABLE 2.—*Short-Term Regimens of Mupirocin for the Treatment of* Staphylococcus aureus *Nasal Carriage*

Source	Treatment Regimen	Treatment Group	No.	S aureus Eliminated at End of Treatment, %	S aureus Eliminated at Follow-up, %
Casewell and Hill, 1985[32]	Daily × 5 days	Hospital staff volunteers	32	100	At 3 mo: 57
Holton et al, 1991[26]	3 × day × 5 days	Hemodialysis patients	22	77	At 1 mo: 46; at 2 mo: 32; at 3 mo: 23
Reagan et al, 1991[19]	2 ×/day × 5 days	Health care workers	34	97	At 3 mo: 71
Redhead et al, 1991[27]	Variable: ≤4 ×/day × 3-5 days*	Hospital inpatients, outpatients, and staff	766	97†	No follow-up cultures
Doebbeling et al, 1992[28]	2 ×/day × 5 days	Healthy volunteers	143	91	At 1 mo: 82
Scully et al, 1992[29]	2 ×/day × 5 days	Healthy medical center staff	34	74	At 1 mo: 41

*Until cultures showed elimination.
†628 patients had methicillin-resistant *S aureus*, which was eliminated in 97%.

One study focused on long-term suppression in hemodialysis patients (Table 3). Mupirocin was applied three times a day for 5 to 14 days and then three times a week (at dialysis) for 6 to 9 months.[17,30] Nasal cultures during this time were negative for *S aureus* in 94% to 100% of the patients. The incidence of *S aureus* bacteremia was reduced 4.26-fold in the carriers treated with mupirocin versus the control group. Only one episode of *S aureus* bacteremia occurred in 41.1 years of patient follow-up in the treatment group (incidence of 0.0227 per patient year) as compared with 18 episodes of *S aureus* bacteremia during 185.8 patient years in the control group (incidence of 0.0969 per patient year; $P = .08$). In another study, the cost of mupirocin prophylaxis was calculated at $266 per patient year, as compared with a cost of $896 per patient year at risk for the treatment of *S aureus* bacteremia. It was concluded that mupirocin prophylaxis is cost-effective.

In studies in Europe, mupirocin resistance did not emerge, despite long-term (9 months) treatment, although resistance has been described by others.[31-33] Low-level resistance is less important because the concentration of mupirocin in the ointment is 20,000 μg per ml. High-level resistance—minimal inhibitory concentration >700 μg per ml—correlates with the clinical failure to eradicate *S aureus*.[34-36] To date, the reported incidence of high-level mupirocin resistance among *S aureus* organisms remains low.[37] Recent reports from hospitals and long-term care facilities in the United States describe both low- and high-level resistance, however.[29,34,38]

Patients on hemodialysis treatment are at an increased risk of *S aureus* colonization with the subsequent complications of vascular access infection, bacteremia, and septic arthritis and attendant dangers of protracted morbidity and mortality. Hence, it seems reasonable to culture the anterior nares of hemodialysis patients periodically (perhaps monthly). In those patients with positive cultures, implementation of the regimen described elsewhere (Table 3)[17,30] may reduce the number of subsequent *S aureus* infections. Patients receiving applications of mupirocin three times a week should have cultures repeated at one- to three-month intervals; if *S aureus* is detected, it is desirable to have the laboratory capability to determine whether mupirocin resistance has developed. Future studies should address the problem of the development of mupirocin resistance and measures that might attenuate the rate of development of resistance in an individual patient or in groups of patients in hemodialysis units.

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TABLE 3.—*Long-Term Regimens of Mupirocin for the Treatment of* Staphylococcus aureus *Nasal Carriage in Hemodialysis Patients*

Source	Treatment Regimen	Hemodialysis Patients, %	S aureus Eliminated With Suppressive Therapy, %
Boelaert et al, 1989[30]	3 ×/day × 2 wk, then 3 ×/wk for 9 mo	16	At 2 wk: 100; during later treatment: 94
Boelaert et al, 1991[17]	3 ×/day × 5 days, then 3 ×/wk for 6 mo	31	At 3 mo: 100; at 6 mo: 100

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